are respectfully requested.

As a preliminary matter, a diskette and paper copy of the sequence listing is being resubmitted herewith as the original sequence listing contained minor errors. The CRF and paper copy of the sequence listing are identical and do not introduce new matter into the application.

As an additional preliminary matter, Applicants are submitting under a separate paper, an Information Disclosure Statement and PTO form 1449 listing references the Examiner is requested to consider in connection with the above-identified application. The requisite fee under 37 C.F.R. §1.17(p) for submission of the statement under 37 C.F.R. §1.97(c) is also submitted herewith.

It is noted that the requirement for restriction set forth by the Examiner in Paper No. 6 has been maintained and made final. Applicants reserve the right to file one or more continuing applications, as provided under 35 U.S.C. §120, on the subject matter of the non-elected claims.

At page 3 of the Official Action, the Examiner has rejected claims 80-82 under 35 U.S.C.§112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to convey to the skilled artisan that the inventor had possession of the invention at the time the application was filed.

The Examiner has also rejected claims 80 and 81 under 35 U.S.C. §102(a) as allegedly anticipated by Hu et al. as evidenced by Jiang et al. and Oikawa et al.

Applicants respectfully submit that the claims as presently amended are in condition for allowance. Each of the above-noted objections and rejections under 35 U.S.C. §112, first paragraph and §102 is, therefore, respectfully traversed.

THE SUBJECT MATTER OF CLAIMS 80-82 FULLY COMPLIES WITH THE WRITTEN DESCRIPTION AND ENABLEMENT REQUIREMENTS OF 35 U.S.C. §112 FIRST PARAGRAPH

The Examiner has rejected claims 80-82 under 35 U.S.C. §112, first paragraph asserting that the specification fails to describe a genus of PI3 kinase inhibitors suitable for use in the instantly claimed method. The Examiner further rejects claim 82 asserting that the specification does not teach any Akt inhibitor nor methods of making such an inhibitor. It is noteworthy, that the specification clearly teaches that molecules which inhibit PI-3 kinase act functionally as PTEN agonists. As the data show, PTEN inhibits activation of Akt, thus a molecule which inhibits PTEN activity, e.g., a PI-3 kinase inhibitor, would in turn act as an inhibitor of phospho-Akt as this molecule is down stream in the signaling pathway. Thus, molecules such as LY294002 act functionally as Akt-inhbitors as well as PI-3 kinase inhibitors.

The Examiner also contends that claim 82 is inadequately enabled by the present specification. Specifically, the Examiner asserts that the specification allegedly fails to 1) teach a single Akt inhibitor, and 2) provide a working example of how to deliver the product to the target site in vivo. Additionally, the Examiner asserts that methods for ~~treating cancer are highly unpredictable and thus undue~~ experimentation would be required to practice the invention as claimed.

The disclosure and data in the application provides clear evidence that Applicant was in possession of the claimed methods as of the filing date of the application. Two PI-3 kinase inhibitors are disclosed which function to inhibit tumor-induced angiogenesis. Several different assays are provided to identify additional putative PI-3 kinase

inhibitors. The written description guidelines set forth in the Federal Register Vol. 66, No. 4, January 5, 2001 are as follows: "An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics, so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention."(page 1105, column 3). "An applicant may also show that an invention is complete by disclosure of sufficiently detailed , relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, ie: complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics." (Page 1106, column 1). Specifically with regard to genus claims, the guidelines state that (2) For each claim drawn to a genus: The written description requirement for a claimed genus may be satisfied through a sufficient description of a representative number of species by actual reduction to practice...reduction to drawings...or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus..." (Page 1106, column 3). Applicant has provided both structural and functional characteristics of the PI-3 inhibitors encompassed by the claims. Nothing more is required under 35 U.S.C. §112, first paragraph.

Akt inhibitors were also known in the art at the time the application was filed. Attached hereto is a copy of an abstract describing such an inhibitor which appeared in the Journal of Biological Chemistry in 1998. As already

mentioned, LY294002 also acts as an Akt inhibitor. A functional assay for assessing activation of Akt is provided in Example I of the specification and the results are shown in Figure 1. It is a well-settled premise in patent law "that a patent need not teach, and preferably omits, what is well known in the art". Lindemann Maschinenfabrik v. American Hoist and Derrick, 221 U.S.P.Q. 481 (Fed. Cir. 1984). Inasmuch as Akt kinase inhibitors were known in the art at the time the application was filed and functional assays are provided for assessing the activity of new Akt inhibitors, Applicant submits that an adequate written description of the method of claim 82 is provided in the present application. Accordingly, it is requested that the rejection of claims 80-82 under 35 U.S.C. §112, first paragraph for inadequate written description be withdrawn.

With respect to the Examiner contention that claim 82 is inadequately enabled by the present specification, Applicant respectfully asserts that Akt inhibitors were known in the art at the time the application was filed and thus a teaching of making such an inhibitor is not required for enablement of a method claims for using the same in the treatment of tumor-induced aberrant angiogenesis. Furthermore, the specification teaches in Example IV that intraperitoneal administration of LY294002 is effective to reduce the growth and incidence of **brain tumors** in a nude mouse model. See Figure 17. Thus, the Examiner's assertion that the specification fails to provide experimental evidence and working examples showing efficacy of the claimed method is erroneous on its face.

In light of all the foregoing, Applicant submits that the presently claimed methods are enabled by the disclosure in the specification and accordingly, request that the rejection of claims 80-82 be withdrawn.

CLAIMS 80 AND 81 ARE NOT ANTICIPATED BY HU ET AL. AS EVIDENCED BY JIANG ET AL. AND OIKAWA ET AL.

In order to constitute evidence of lack of novelty under 35 U.S.C. §102(b), a prior art reference must identically disclose each and every element of the rejected claim. In re Bond, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). Applicants respectfully assert that the claims as presently amended are not anticipated by the disclosure in the Hu et al. reference.

Claim 80 is directed to a method for inhibiting tumor-induced aberrant **angiogenesis** via the administration of a PI-3 kinase inhibitor to a patient in need thereof. Hu et al. teach that LY294002 inhibits growth of ovarian carcinoma cells via the promotion of apotosis. Indeed the growth of the tumors described by Hu et al. were assessed via measuring increases in ascites fluid volume where very little tumor induced angiogenesis is occurring. Inasmuch as Hu et al. fail to teach this aspect of the present method, it cannot be reasonably maintained that Hu et al. anticipate the claimed invention.

The Examiner relies on the Oikawa et al. reference as "evidence" in support of the §102 rejection of claims 81 and 82. The Examiner's attention is drawn to page 95, second column of this reference wherein the authors disclose:

"Taken together **it seems reasonable to speculate** that wortmannin influences in vivo angiogenesis through inhibition of phosphotidylinositol 3-kinase, although the possibility that other molecule(s) may be a target cannot be completely excluded, because there is one report suggesting that this microbial product may affect phospholipase A2, at low nanomolar concentrations (Cross et al. 1995).

If the above speculation is true..."

The foregoing disclosure highlights the uncertainty of Oikawa et al. regarding whether wortmannin acted through PI-3

kinase or phospholipase A2. Accordingly, the Examiner's reliance on this reference as "evidence" of anticipation is misplaced.

The §102(a) rejection based on Hu et al. as evidenced by Jiang et al. or Oikawa et al. reference should be withdrawn for the additional reason that the Hu et al. reference is not properly citable against the claims of this application. Under the Patent and Trademark rules of practice, when any claim of a U.S. patent application is rejected on reference to a printed publication, the timely filing of a Declaration showing conception of the invention prior to the effective date of the reference followed by a diligent reduction to practice in this country, will remove the publication as a bar to the grant of a patent to the inventor. 37 C.F.R. §1.131(a).

Pursuant to 37 C.F.R. §1.131, there is submitted herewith a Declaration of Dr. Durden which clearly establishes conception prior to the March 2000 and February 2000 publication dates of the Hu et al. and Jiang et al. references.

The data presented in the Exhibits accompanying the Declaration of Dr. Durden provide clear evidence of the inventors' recognition of the anti-angiogenesis effects of PI-3 kinase inhibitors. Specifically, the disclosure in Exhibit A provides evidence of conception of Applicant's invention prior to the March 2000 publication date of the Hu et al. reference.

The data presented in Exhibits B, C and D clearly demonstrate reduction to practice of the present invention wherein the anti-angiogenesis effects of wortmannin and LY294002 were tested. See Exhibit C, Figures 10, 14, 15 and 16. The results presented in Exhibit C demonstrate that administration of a PI-3 inhibitor was successful in inhibiting tumor-induced angiogenesis in a nude mouse model.

In summary, Applicant's Exhibit A shows the conception of

the methods of the present invention. Exhibits B-D provide data showing that the present invention was reduced to practice.

In view of the clear evidence of conception prior to the publication date of Hu et al. and the diligent reduction to practice of the present invention as set forth in the Declaration of Dr. Durden, the §102 rejection's reliance on the Hu et al. reference is improper. This rejection should, therefore, be withdrawn.

In view of the present amendments, the declaration submitted herewith and the foregoing remarks, it is respectfully urged that this application be passed to issue and such action is earnestly solicited.

Respectfully submitted,

DANN, DORFMAN, HERRELL AND SKILLMAN
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Enclosures: Abstract describing Akt inhibitor
Revised Sequence listing

Marked up draft of amended specification

In the specification:

(Page 2, line 23) PTEN is a 55 kDa protein comprising an N-terminal catalytic domain, identified as a segment with homology to the cytoskeletal protein tensin and containing the sequence $HC(X)_5R$ (SEQ ID NO: 22), which is the signature motif of members of the protein tyrosine phosphatase family, and a C-terminal C2 domain with lipid-binding and membrane-targeting functions (Lee et al Cell 1999). The sequence at the extreme C-terminus of PTEN is similar to sequences known to have binding affinity for PDZ domain-containing proteins. PTEN is a dual specificity phosphatase that displays a pronounced preference for acidic substrates (Myers et al PNAS 1997).

(Page 15, line 9) Figure[s] 20A is a schematic representation of PTEN. A PTEN sequence (SEQ ID NO: 23) which matches the signature sequence motif of protein tyrosine phosphatases is also shown. [and] Figure 20B depicts a PTEN encoding nucleic acid (SEQ ID NO: 1; shown in double-stranded form) and the amino acid sequence (SEQ ID NO: 2) of PTEN [, respectively].

(Page 27, line 18) The PTEN protein comprises, from amino- to carboxy-terminus, a protein tyrosine phosphatase catalytic domain that has considerable homology to the cytoskeletal protein tensin, a C2 domain that confers lipid-binding and membrane-targeting, and a PDZ domain-binding site that contributes to membrane localization and protein stability (Lee et al Cell 1999, Wu et al PNAS 2000;). The amino-terminal catalytic domain includes the $HC(X)_5R$ sequence (SEQ ID NO: 22), which is the signature motif of protein tyrosine phosphatases. The Genbank accession number for the human PTEN encoding nucleic acid molecule is NM000313. The

amino acid sequence of PTEN is provided in Figure 20B. These sequences are also referred to herein as SEQ ID NO: 1 and SEQ ID NO: 2.

(Page 44, line 19)

TABLE I

PTEN peptide motifs used to screen for PTEN agonists and inhibitors

Phosphorylation site motifs:	**amino acid residue number**	
DLDLT**Y**IYP	(22-30)	SEQ ID NO: 3
YLVLTL	(27-30)	SEQ ID NO: 6
YRNNIDD	(46-52)	SEQ ID NO: 8
KGVTIP**S**QR**RY**VYYYS**Y**LL	(164-182)	SEQ ID NO: 15
YSYL	(178-181)	SEQ ID NO: 7
YFSPN	(336-339)	SEQ ID NO: 5
RY**S**D**TT**DS	(378-385)	SEQ ID NO: 16
Catalytic Domain motifs	**(1-185)**	
H**C**K**A**GK**G**R(P-loop)	(123-130)	SEQ ID NO: 9
DHNPPQ (WPD-loop)	(92-97)	SEQ ID NO: 10
KGVTIP**S**QR**RY** (TI-loop)	(164-174)	SEQ ID NO:17
C2 domain motifs	**(186-350)**	
HF**W**VNT**FF**I	(272-280)	SEQ ID NO: 11
C terminal tail related regions of interest	**(351-403)**	
TLTKNDLD---FTK**T**V(PEST domain sequences)	(319-351)	SEQ ID NO: 12

GDIKVEF---FTKT**V** (PEST domain sequences) (251-351)

SEQ ID NO: 13

DKANKDKAN---FTKT**V** (PEST) (331-351)

SEQ ID NO: 14

RY**S**D**TT**DS (pre-PDZ region) (378-385)

SEQ ID NO: 16

HTQITKV (PDZ-MAGI-2 interaction domain) (399-403)

SEQ ID NO: 18

Claim amendments

80. (Amended) A method for inhibiting aberrant tumor-induced angiogenesis in a patient in need thereof, said method comprising the administration of a PI-3 kinase inhibitor.

1: J Biol Chem. 1998 Jun 26;273(26):16568-75.

Related Articles, Links

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Inhibition of Akt kinase by cell-permeable ceramide and its implications for ceramide-induced apoptosis.

PubMed Services

Zhou H, Summers SA, Birnbaum MJ, Pittman RN.

Department of Pharmacology, and Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.

Related Resources

Ceramide is an important lipid messenger involved in mediating a variety of cell functions including apoptosis. However, mechanisms responsible for ceramide-induced apoptosis remain unclear. We investigated the possibility that ceramide may decrease antiapoptotic signaling in cells by inhibiting Akt kinase activity. Our data show that C2-ceramide induces apoptosis in HMN1 motor neuron cells and decreases both basal and insulin- or serum-stimulated Akt kinase activity 65-70%. These results are consistent with decreased Akt kinase activity being involved in the apoptotic effects of ceramide. This possibility is further supported by studies showing that constitutively active Akt kinase decreases C2-ceramide-induced death of HMN1 cells as well as COS-7 cells. Decreased Akt activity is not due to ceramide activating the ceramide-activated protein phosphatase or to a direct inhibition of Akt kinase by ceramide, suggesting that ceramide acts upstream of Akt kinase to decrease its activity. Treating cells with C2-ceramide does not affect phosphorylation of insulin receptor substrate-1, interactions between insulin receptor substrate-1 and p85, or insulin-stimulated phosphatidylinositol 3-kinase activity, suggesting that the effects of C2-ceramide on Akt kinase are not mediated through modulating phosphatidylinositol 3-kinase. In sum, our results suggest that inhibition of the key antiapoptotic kinase, Akt, may play an important role in ceramide-induced apoptosis.

PMID: 9632728 [PubMed - indexed for MEDLINE]